REMARKS

Claims 1-20 are pending. The claims have been amended to be placed in more typical U.S. format Support for the amendment to claim 10 may be found in Example 7 at pages 9-11 of the specification. None of the amendments constitutes new matter.

The claims have been rejected under 35 U.S.C. §101, §112, and/or §103. For reasons to be set forth below, it is respectfully requested that these rejections be withdrawn and that the claims be allowed.

1. **The Claims Are Not Indefinite**

Claims 1-20 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner contends that (1) the term "deep frozen", as recited in claims 1, 6 and 12, is unclear and "[t]he claims are indefinite as to the freezing temperature employed for freezing the thrombocytes or thrombocyte fragment"; (2) claim 2 recites both the broad limitation of at least 10^4 thrombocytes per milliliter as well as the narrower range of at least 10^5 thrombocytes per milliliter, so that the limitation in the claim is uncertain; and (3) claim 10 provides for the use of thrombocytes or thrombocyte fragments containing growth factors but because there are no active, positive steps it is unclear what method or process Applicants intend to encompass.

In response, Applicants assert that the skilled artisan would not find the term "deep frozen" to be indefinite. Blood components are routinely frozen for preservation. It would

be apparent to the person skilled in the art that freezing may occur at any temperature at or below the freezing point of the components. Although the specification, in its working examples, mentions that thrombocytes had been frozen at -80 °C (*see,*, for example, the specification at page 7 lines 12 and 15), the claims should not be so restricted as clearly thrombocytes, which are largely water-based, could be frozen at either warmer or colder temperatures. Accordingly, Applicants contend that no amendment of the term "deep frozen" is necessary.

Claim 2 has been amended to delete the narrower limitation of the preferred embodiment wherein at least 10^5 thrombocytes per milliliter are present, thereby obviating the basis for the rejection.

Claim 10, which had originally been drafted in European style, has been amended to have the format of a typical method of treatment claim and to contain the positive step of "applying to the wound a composition comprising thrombocytes or thrombocyte fragments containing growth factors and capable of releasing the same".

For the foregoing reasons, the rejections under 35 U.S.C. § 112 should be withdrawn.

2. Claim 10 Constitutes Statutory Subject Matter

Claim 10 is rejected under 35 U.S.C. §101 because, according to the Examiner, the "recitation of a use, without setting forth any steps involved in the process, results in an

improper definition of a process". Because claim 10 has been amended to recite an active step, this rejection should be withdrawn.

3. The Claims Are Not Obvious

Claims 1-20 are rejected under 35 U.S.C. §103(a) as obvious over Patat et al., United States Patent No. 5,589,462 ("Patat") in view of Delmas, United States Patent No. 5,618,663 ("Delmas"), Dimoudis et al., 1996, CA Abstract, AN 1996:313895 ("Dimoudis") and Goodrich et al., WO 91/17655 ("Goodrich").

The Examiner contends that Patat teaches a medicinal product for topical promotion of wound healing that comprises frozen growth factor containing thrombocytes. The Examiner further contends that although Patat does not expressly teach inactivation of viruses or the utilization of other cell types or liposomes, Delmas teaches inactivation of viruses in thrombocyte products for healing, Goodrich teaches lyophilization of platelets in therapeutic compositions, and Dimoudis teaches that epithelial cells are known to be useful in wound healing compositions. The Examiner concludes that

> it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to modify the platelet factor enriched thrombocyte compositions of Patat et al. with the inactivation of viruses present with thrombocyte [*sic*] taught by Delmas, and lyophilization taught by Goodrich and by the addition of other known wound healing components such as epithelial cell [*sic*].

According to the Examiner, the skilled artisan would have been motivated to inactivate viruses in order to avoid transmission of disease, would have utilized epithelial cells in the compositions in

view of the known usefulness of such cells in wound healing compositions, and would have lyophilized platelets because platelets preserved in this manner may be stored at high temperatures and then reconstituted.

Applicants respectfully assert that the claimed invention is not obvious over any of the cited references or any combination thereof. The present invention relates to therapeutic compositions and methods wherein thrombocytes (a.k.a. platelets) containing growth factors are applied to a wound such that they release growth factors over time. The specification states, at page 4 lines 8 - 20:

> The invention is based on the finding that the topical use of thrombocytes containing growth factors and capable of releasing the same can efficaciously accelerate wound healing processes. The thrombocytes applied on the wound area constitute a natural reservoir for the growth factors required for the promotion of wound healing processes. It has been found that the activation of locally applied thrombocytes by physiological stimuli present in the wound area lead the growth factors stored in the thrombocytes to be released into the wound continuously over an extended period of time (several days). Due to this fact, higher concentrations of growth factors are apparently [available] in the wound area over a substantially longer period of time than with the direct administration of growth factors, thereby promoting the immigration of inflammatory cells, connective tissue cells and endothelial cells and enhancing the propagation of said cells in stage II of the wound healing process.

Example 6 of the specification at page 9, lines 15-26 shows that growth factor release was blocked by specific antibodies directed toward the superficial binding sites for thrombocytes on matrix proteins, showing that "the binding of matrix proteins to the thrombocyte surfaces is necessary for the thrombocyte stored growth factors to be released". Example 5 of the specification at page 8 line 25 through page 9 line 14 demonstrated that release

of growth factors occurred over an extended period of time. The foregoing data suggests that, as claimed, the compositions of the invention comprise thrombocytes which provide a sustained release of growth factors.

In contrast to the present invention, the critical teaching of Patat is the use of a cryoprecipitate prepared under extremely specific temperature conditions. Patat states:

> The biological adhesive according to the invention may essentially consist of a cryoprecipiate derived from a platelet-enriched plasma . . . (Patat, column 4 lines 13-15); and
>
> It is known that the preparation of a cryoprecipitate consists in freezing a plasma and then in thawing it at room temperature greater than 0 and less than 6°C, generally between +1°C and +4°C. The solid fraction which remains, and which contains especially fibrinogen and fibronectin, is called cryoprecipitate and can be separated from the liquid fraction by centrifugation. (Patat, column 2 lines 31-38)

The instant disclosure, by not requiring that such a cryoprecipitate be prepared, teaches against Patat, which mandates cryoprecipitate preparation.

Furthermore, Delmas, contrary to the Examiner's assertion, does not relate to viral inactivation of thrombocytes or fragments which are insoluble and sedimentable, but rather to viral inactivation of a *supernatant containing soluble growth factors which are not sedimentable by centrifugation*. This is made clear at column 6, lines 35-46 of Delmas, which state:

> The supernatant (12) can be subjected to a viral inactivation stage, either by pasteurization by immersion in a water bath under validated conditions, or by neutralizing antibodies, or by filtration (Virosolve system developed by Millipore, Bedford, U.S.A.; Asahi system, Pall system) or by any other method which is effective in decreasing the [viral] load while retaining a sufficient activity in the treated product. The viral inactivation system can be produced so as to be made integral with the device described above and consequently to retain the closed nature of the said device.

It should be noted that certain of these methods, such as pasteurization, are only suitable for soluble substances, and therefore, while they may be appropriate for treating the supernatant of Delmas, they would not be suitable for treating the insoluble thrombocytes and fragments of the invention. The use of a supernatant is an essential feature of Delmas, which teaches that platelets should be activated so as to release soluble factors which are separated by filtration or centrifugation from platelets or platelet fragments:

> The subject of the invention is a method for obtaining a solution of platelet factors comprising a stage of thrombocyte activation by bringing into contact with a thrombocyte activator solution, and in which a solution of platelet factors released by the thrombocytes during the activation stage is collected, characterized in that a liquid containing a suspension of thrombocytes is passed through a filter capable of retaining the thrombocytes, in that an activator solution is added to the thrombocytes retained on the filter and in that a filtrate containing the platelet factors in solution is separated by filtration whereas the thrombocytes remain retained on the filter.
>
> (Delmas, column 2, lines 41-52)

Thus, Delmas teaches <u>against</u> compositions comprising thrombocytes, and teaches against the use of thrombocyte factors in sustained releasable form. Because Delmas teaches against the key features of the present invention, it cannot render the claims obvious. Furthermore, it is improper to consider Delmas only as it relates to viral inactivation and to ignore the full content of its disclosure.

The teachings of Dimoudis and Goodrich are even more peripheral to the inventive concept of the present claims, as the references relates merely to the use of epithelial cells and lyophilization techniques, rather than the use of growth factor-containing thrombocytes

for promoting wound healing. Accordingly, the addition of their disclosures to those of Patat and/or Delmas fails to render the claims obvious.

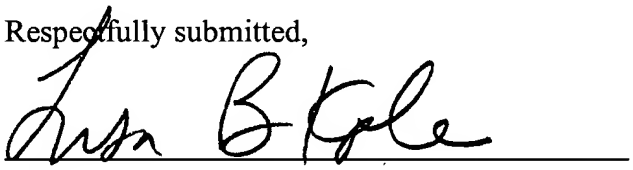
Therefore, neither any one of the cited references nor any combination thereof renders the claims obvious, so that the pending rejection should be withdrawn.

CONCLUSION

For all the foregoing reasons, it is respectfully requested that the rejections be withdrawn and that the claims be allowed to issue.

An early allowance is earnestly requested.

Respectfully submitted,



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